

Virotherapy in spotlight again, in use at bedside

A recent phone call from an editor at *Scientific American* brought some news to UAB researcher David Curiel, M.D., Ph.D., and Ronald Alvarez, M.D., professor of Obstetrics & Gynecology.

The internationally renowned magazine selected a story on a virotherapy, authored by Curiel and Alvarez and originally published in the magazine in October 2003, as one of 10 groundbreaking stories of the past 10 years. The magazine reprinted the article for its summer 2008 edition.



David Curiel (above) and Ronald Alvarez have taken their virotherapy idea from bench to bedside — and are testing its safety in patients — in less than five years.

“They said they were compiling the most interesting articles of the past 10 years,” Curiel says, “and they wanted to re-issue our article. We’re excited that they picked our story, and we’ve also come a long way since the article was originally published.”

Indeed since publishing on the technique of virotherapy and its role in battling cancer, Curiel and Alvarez have taken the idea from bench to bedside and are testing its safety in patients at UAB with ovarian cancer.

“In five years we went from idea, to proof of principle, to validation in model system, to regulatory approvals to human trials,” Curiel says. “Drugs with pharmacy companies can take 20 years to develop, so this is a very compressed timeline.”

What is virotherapy?

Virotherapy is a targeted therapy in which a virus is altered and programmed in the laboratory to find and destroy cancer cells without harming healthy cells. Curiel and his researchers have drastically altered the adenovirus virus — the virus that causes the common cold — turning it into search-and-destroy missiles, selectively infecting and killing cancer cells while leaving healthy ones alone. This is being tested on 10 patients and represents the first point of departure for virotherapy in which the virus has been altered in a fundamental way, used in treatment and found to be safe.

“We radically altered a virus design to improve its utility, and we were able to get that into patients quickly because we provided all of the data that validated their safety,” Curiel says.

UAB researchers have opened the door for new, radical virus designs that will be useful to humans in the process.

“It’s like when you first break gravity; once you know you can do it, it becomes easier the next time,” Curiel says. “The next people who want to come with radically altered viruses will have this as their point of departure.”

The perfect delivery device

Fundamental to achieving gene therapy is the ability to re-engineer a virus to infect the target cell. “In other words, one could argue if you’re faced with the problem of gene delivery, God made the most perfect device to do that — a virus.”

The virus has evolved over millennia and is extremely effective at delivering genes. Treatments using viruses worked well with animal models in early gene-therapy testing, but human trial results weren’t as fortunate. The viruses didn’t infect humans quite as well as it did in the animal models.

Researchers and physicians around the country were using the adenovirus for virotherapy, so Curiel’s team wanted to modify the way the virus binds to a cell, making it more infectious. Many people believed the common cold virus already had evolved to be as infectious as it could be. But researchers here were able to make genetic changes in the code protein, and make the virus stick to the cell more efficiently to improve its effectiveness.

“Normally when we improve a cancer drug, if it works two times better or three times better, that’s sufficient to justify a whole new clinical trial,” Curiel says. “We were able to improve its efficiency 10,000-fold. It was a substantial advancement in effectiveness.”

A human trial was the next logical step, and if researchers could engineer the virus to replicate only in cancer cells and kill only cancer cells, that would be a promising targeted therapy.

UAB collaborated with a group at M.D. Anderson Cancer Center that was using a virotherapy approach for a glioma brain cancer to try to improve their virus by infectivity enhancement. The new version of the virus achieved therapies in their animal models of brain cancer that exceeded any therapy they had tested before.

A three-institution consortium was then formed among UAB, M.D. Anderson and Erasmus University in Rotterdam, Netherlands, to test the safety of the therapy in humans. UAB began testing earlier this year, and Curiel says M.D. Anderson and Erasmus University will begin testing “any day now.”

Close scrutiny

Curiel says more than 300 gene-therapy trials have taken place in recent years, and thousands of patients have been treated with a viral vaccine agent. But the virus had never been altered in any of those trials. Because this would be the first trial in which a

virus had been fundamentally altered to change how it entered the cell, it was under close scrutiny by the federal government.

The Southern Research Institute aided Curiel's team in developing a safety profile for the treatment and the government endorsed the trial. Alvarez has since treated 10 of planned 12 patients for ovarian cancer.

"So far a very encouraging safety profile has been demonstrated," Curiel says. "This radical new virus that is so extremely potent doesn't appear to have limiting toxicities that we've been able to see."

The virus is administered to the patients directly into the perineum through a catheter, enabling Alvarez to deliver the virus directly into the tumor.

While this trial is primarily focused on the safety of the procedure, other data is being collected to be analyzed, including checking if the tumor size for changes.

"People always want to know if it's working clinically yet, but it's too early into the trial to be able to say that," Curiel says. "The thing we can say immediately is that it's not toxic, and that is extremely encouraging."

Prompting innovation

Because the virotherapy is non-toxic it enables researchers to advance the dose of the virus and enables them to consider future designs of the virus to improve it further.

UAB's need to get as much information from this trial as it can has led to the development of imaging systems. Researchers will be able to place an imaging motif on the virus, enabling them to monitor its effectiveness in ways that have never happened in clinical research.

"We've made the viruses have the ability to give imaging signals so that simultaneous with therapy, we can monitor the viruses location and distribution," Curiel says.

"Ronnie and I have been funded for that, so our next generation trials will embody imaging which we think will give us even more useful information."

The National Cancer Institute and Rapid Access for Interventional Development have funded these projects "about as aggressively as they can," Curiel says. "It's our hope that now that you can use advanced generational viruses and people are comfortable with them that it will open up all kinds of possibilities."

Cancer virotherapies developed for canines, too

UAB researcher David Curiel, M.D., Ph.D., says the most rapid growth in the veterinary market is canine cancer. The desire for cheaper, new, effective and innovative ways to treat dogs has aided UAB's virotherapy ovarian cancer research in its move from bench to bedside in less than five years.

UAB developed a relationship with Auburn University's veterinary school during the course of its work in virotherapy research and has forged a partnership that both sides hope will help canines with cancer.

"The three most common tumors in dogs are the precise mimics of their human counterparts," Curiel says. "They get skin cancer, lymphoma and bone cancer. Just like there is a human adenovirus there is a canine adenovirus. We've been working with Auburn's veterinary school to engineer the canine adenovirus, make virotherapy agents and treat dogs just like we do patients in clinical trials."

This has enabled researchers to find treatments for humans and canines faster and given them data that's helped design human agents.

"I'm certainly learning a lot about dogs," Curiel says.

There are very few cancer treatment options for canines that are effective, Curiel says. Many canine cancer therapies are holistic in nature.

"There are virtually no therapies for canine cancer," Curiel says. "We're developing things in our research with humans that we hope will end up being therapies for dogs as well."

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